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ORIGINAL ARTICLE

A real-life study of the medium to long-term effectiveness of a hypercaloric, hyperproteic enteral nutrition formula specifically for patients with diabetes on biochemical parameters of metabolic control and nutritional status☆

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KEYWORDS
Enteral nutrition;
Specific enteral formula for diabetes;
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Abstract:
Introduction: Although current recommendations suggest the use of specific formulas in enteral nutrition in people with diabetes, there is little evidence of their long-term effectiveness in glycemic control. The main objective of this study is to evaluate the long-term efficacy (24 weeks) of a specific high-protein hypercaloric enteral nutrition formula for people with diabetes in glycemic control and in their improvement in nutritional status.
Methodology: This was a multicenter, prospective, observational, real-life study of patients with long-term enteral nutrition prescription through gastrostomy or nasogastric tube who received a high protein hypercaloric formula specific for diabetes. Once the participant's informed consent was obtained and the inclusion and exclusion criteria were verified, data relating to glycemic control, inflammation parameters, biochemical data, nutritional status and gastrointestinal tolerance at 0, 12 and 24 weeks were collected.
Results: 112 patients were recruited, 44.6% women, age 75.0 (12.0) years and a mean time of evolution of diabetes of 18.1 (9.5) years. The percentage of patients with malnutrition according to VGS decreased throughout the treatment from 78.6% to 29.9% ($p < 0.001$). Glycemic and HbA1c levels were significantly reduced at 12 and 24 weeks (Blood glucose 155.9–139.0–133.9 mg/dl, $p < 0.001$; HbA1c 7.7–7.3–7.1%, $p < 0.001$) while no significant changes were observed in cholesterol, triglycerides, creatinine, or glomerular filtration. A significant increase in variables related to nutritional status was observed: weight, the BMI, albumin, prealbumin and transferrin, and CRP levels were significantly reduced and the CRP/Albumin ratio decreased. Gastrointestinal tolerance was good, the number of patients with moderate-severe symptoms was small, and did not change throughout the follow-up.
Conclusion: Our real-life study suggests that the use of a specific hyperprotein hypercaloric formula for diabetes during a 6-month nutritional treatment allows adequate glycemic control and nutritional evolution, with good gastrointestinal tolerance.

PALABRAS CLAVE
Nutrición enteral;
Fórmula enteral específica para diabetes;
HbA1c;
Desnutrición;
Diabetes

Estudio en vida real de la efectividad a medio-largo plazo en parámetros bioquímicos de control metabólico y estado nutricional de una fórmula de nutrición enteral hipercalórica hiperproteica específica para pacientes con diabetes

Resumen
Introducción: Aunque las recomendaciones actuales sugieren el empleo de fórmulas específicas en nutrición enteral en personas con diabetes, hay poca evidencia de su efectividad a largo plazo en el control glucémico. El objetivo principal de este estudio es evaluar la eficacia a largo plazo (24 semanas) de una fórmula de nutrición enteral hipercalórica hiperproteica específica para personas con diabetes en control glucémico y mejora del estado nutricional.
Metodología: Estudio multicéntrico observacional prospectivo en vida real de pacientes con prescripción de nutrición enteral de larga duración a través de sonda de gastrostomía o nasogástrica que recibieron una fórmula hipercalórica hiperproteica específica para diabetes. Una vez obtenido el consentimiento informado del participante y comprobados los criterios de inclusión y exclusión, se recogieron datos relativos a control glucémico, parámetros de inflamación, bioquímicos, situación nutricional y tolerancia gastrointestinal a 0, 12 y 24 semanas.
Resultados: Se reclutaron 112 pacientes, 44,6% mujeres, edad 75,0 (12,0) años y tiempo medio de evolución de la diabetes 18,1 (9,5) años. El porcentaje de pacientes con desnutrición según VGS descendió a lo largo del tratamiento de 78,6% a 29,9% ($p < 0,001$). Los niveles de glucemia y de HbA1c se redujeron significativamente a las 12 y 24 semanas (Glucemia 155,9–139,0–133,9 mg/dl, $p < 0,001$; HbA1c 7,7–7,3–7,1%, $p < 0,001$) mientras que no se observaron cambios significativos en colesterol, triglicéridos, creatinina ni filtrado glomerular. Se observó un aumento significativo de las variables relacionadas con la situación nutricional (peso, IMC, albúmina, prealbúmina y transferrina), se redujeron significativamente los niveles de PCR y disminuyó el cociente PCR/Albúmina. La tolerancia gastrointestinal fue buena, siendo escaso el número de pacientes con síntomas moderados-graves y no se modificó a lo largo del seguimiento.
Conclusión: Nuestro estudio en vida real apoya que el empleo de una fórmula hipercalórica hiperproteica específica para diabetes durante un tratamiento nutricional a 6 meses permite un adecuado control glucémico y evolución nutricional, con una buena tolerancia gastrointestinal.

Introduction

Hyperglycaemia is a problem associated with type 1 and 2 diabetes mellitus (DM). In the short term, prolonged hyperglycaemia can cause polyuria, increased thirst, dehydration, involuntary weight loss and asthenia, and lead to severe acute complications, such as ketoacidosis or a hyperosmolar state. In the long term, the complications can be more serious, such as microvascular lesions (retinopathy, polyneuropathy or diabetic nephropathy) or macrovascular lesions (including stroke, acute myocardial infarction and peripheral vascular disease). High blood glucose levels for long periods have also been associated with an increased risk of infection and delayed wound healing. To improve blood glucose control, in addition to fasting glucose concentrations, it is also important to monitor postprandial blood glucose levels. Maintaining normal glucose levels is one of the main goals of any therapy in patients with diabetes. Food and nutrition play a fundamental role in these patients.

For patients with diabetes who need to spend long periods receiving enteral nutrition (EN), prescribing a specific high-protein, high-calorie EN formula should be considered for the metabolic control of their diabetes.[1] Several studies have shown the effectiveness of these formulations in controlling basal blood glucose in short and intermediate-length periods (<12 weeks) in patients with DM.[2,3] However, there is little evidence on the effectiveness of these formulations in the long term (>6 months) on basal and postprandial blood glucose control, the improvement or maintenance of nutritional status, or changes in biochemical parameters of inflammation. The main aim of this study was therefore to evaluate the long-term efficacy (24 weeks) of a specific high-protein, high-calorie EN formula for people with diabetes in terms of blood glucose control, evaluated by glycated haemoglobin (HbA1c), biochemical parameters of inflammation and changes in nutritional status over a six-month period. In addition, a secondary objective was to analyse the degree of gastrointestinal tolerance of the administered EN formula.

Methods

This was a real-life, prospective, observational, multicentre study of patients prescribed long-term EN at home, either through gastrostomy tube or nasogastric tube. The study was approved by the Independent Ethics Committee of the Complejo Asistencial Universitario de León, Léon, Spain (study 1629, approval date 29 March 2016) and was conducted in compliance with the ethical and legal standards required for biomedical research according to the Declaration of Helsinki. All the patients included gave their written informed consent.

The centres participating in the study received an invitation to participate from the principal investigator, but no randomisation method was followed as it was a real-life observational study. The collaborating investigators were asked to consecutively enrol in the study all patients who met the inclusion criteria during the study period (from 9 May 2016 to 31 December 2019): over 40 years of age with a history of type 2 diabetes diagnosed prior to the current episode; with HbA1c levels $\geq$7.0% and <10%; who were prescribed enteral nutrition (through a nasogastric tube or gastrostomy) with an expected duration of 24 weeks or longer. The patient or their main caregiver had to be able to understand the study and be completely free to decide whether to participate or not, as well as sign the informed consent form. Patients were excluded if they met any of the following criteria: known allergy to any of the product's ingredients; severe kidney or liver disease (glomerular filtration rate less than 30 ml/min, transaminase elevation $\times$ 3 upper limit of normal); NYHA grade IV heart failure; treatment with corticosteroids (2 weeks before and at any time during the study period); gastrointestinal disease, either active or in the 2 weeks before the start of the study; contraindication to the use of fibre; poor blood glucose control (HbA1c >10%); hospital admission; pregnancy; or breast-feeding. As this was an observational study under real clinical practice conditions, the patients followed the EN regimen recommended by their treating physician to cover their energy and macronutrient needs according to the usual clinical practice of the participating centres. The specific treatment of diabetes was also left to the discretion of the investigating physicians. The high-calorie, high-protein formula used to cover these needs had a calorie density of 1.5 Kcal/mL and was composed of 20% proteins (7.5 g/100 ml), 35% carbohydrates (13.1 g/100 ml, maltodextrin, tapioca dextrin, isomaltulose and fructose), 3% fibre (2.3 g/100 ml, 78% soluble) and 42% fats (7 g/100 ml, rapeseed, sunflower and soybean vegetable oils, medium-chain triglycerides [MCT] and fish oil).

The sample size was pre-determined using the change in HbA1c in patients consuming the EN formula administered for 24 weeks. Considering that we estimated an improvement in HbA1c levels of 0.8%, assuming, in a two-tailed comparison, an alpha error (type I) of 5%, a beta error of 20% and 15% losses to follow-up, a total sample size of 44 patients was calculated to conduct the study. It was subsequently decided to enlarge the sample in order to also have sufficient statistical power to assess the secondary endpoints. A paper-format case report form (CRF) was created to record the data. Once the informed consent of the participant had been obtained and the inclusion and exclusion criteria verified, the following data was recorded anonymously on the case report form (CRF) at the recruitment visit: their personal details (age and gender); concomitant diseases and treatments; place of residence (home or institution); data on diabetes (time since onset, complications, treatment and episodes of hypoglycaemia); reason for EN prescription and dose and route of administration; initial anthropometric characteristics (height, weight); and subjective global assessment (SGA). Basal blood glucose levels, HbA1c, total cholesterol, triglycerides, creatinine and glomerular filtration rate, albumin, prealbumin, transferrin and C-reactive protein (CRP) were all recorded.

The successive visits were carried out under normal clinical practice conditions at 12 and 24 weeks from the start of treatment. The same anthropometric, SGA and biochemical data were collected at these visits, as well as changes in disorders suffered and concomitant treatments, and episodes of hypoglycaemia per month. Gastrointestinal tolerance was assessed considering the percentage of patients who developed the following symptoms: nausea, vomiting, regurgitation, constipation, diarrhoea, flatulence,

Table 1 Baseline characteristics and changes at 12 and 24 weeks.

Visits	Baseline	12 weeks	24 weeks
Subjective global assessment B–C (%)	78.6	68.5*	29.9*
Weight (kg)	59.6 (11.5)	60.9 (11.2)*	61.9 (11.9)*
BMI (kg/m^2)	22.3 (3.5)	22.7 (3.4)*	23.0 (3.6)*
Amount of formula prescribed (ml/day)	1,195.8 (312.9)	1,189.3 (333.9)	1,184.2 (372.1)
Blood glucose (mg/dl)	155.9 (48.2)	139.0 (37.1)*	133.9 (38.8)*
HbA1c (%)	7.7 (0.8)	7.3 (0.7)*	7.1 (0.7)*
Hypoglycaemia episodes/month (n)	0.04 (0.24)	0.37 (0.88)	0.20 (0.66)
Creatinine (mg/dl)	1.08 (0.73)	1.03 (0.47)	1.03 (1.84)
Glomerular filtration rate (ml/min)	80.1 (6.1)	75.9 (6.1)	74.4 (6.1)
Total cholesterol (mg/dl)	165.9 (28.6)	167.2 (26.6)	164.5 (25.6)
Triglycerides (mg/dl)	124.7 (55.7)	126.7 (41.1)	124.8 (25.6)
Albumin (g/dl)	2.8 (0.4)	3.2 (0.4)*	3.4 (0.4)*
Prealbumin (g/dl)	15.4 (3.7)	19.9 (2.6)*	23.3 (3.1)*
Transferrin (mg/dl)	193.2 (44.4)	197.3 (40.3)*	230.1 (59.9)*
CRP (mg/dl)	25.5 (47.4)	9.4 (19.2)*	9.2 (18.9)*
CRP/albumin (mg/g)	10.3 (20.2)	2.9 (5.9)*	2.8 (5.8)*

BMI: body mass index; CRP: C-reactive protein; HbA1c: glycated haemoglobin.
* $p < 0.001$.

abdominal distension and abdominal pain. They were considered mild if the symptom was present but not bothersome; moderate if the symptom was frequently bothersome but did not interfere with daily activities or sleep; severe when it was bothersome enough to interfere with daily activities or sleep; and very severe when it required medical attention.

All data were recorded in a database created solely for the study in Microsoft Excel 97-2003 (© Microsoft). All the analyses were carried out using the statistical program SPSS version 24 (IBM Corp©). Data analysis was only performed for existing data, with no substitution for missing data. For the statistical analyses, statistics of central tendency were used to describe the variables (mean [standard deviation]), as the normality tests indicated that the data were distributed according to a normal distribution (Kolmogorov–Smirnov and Shapiro–Wilk tests). Qualitative variables are described by frequency and percentage. To assess whether there were significant differences during the treatment period (baseline visit, 12 and 24 weeks), a general linear model for repeated measures (repeated measures ANOVA) was used for the quantitative variables (weight, BMI and biochemical data) and the comparison of paired proportions test (McNemar test) for qualitative variables (change in nutritional status). The level of significance used was 5% ($p < 0.05$).

Results

A total of 112 patients were recruited for the study, 50 women (44.6%) and 62 men (55.4%). All patients who met the inclusion criteria during the follow-up period at the participating centres agreed to participate and all completed the 24-week follow-up. The mean age was 75.0 (12.0) years, 41.2% lived in their own home and 58.8% lived in institutions. The mean time since onset of diabetes was 18.1 (9.5) years. With regard to diabetes-related complications, 43.8% had retinopathy, 26.8% polyneuropathy, 25% nephropathy and 25% cardiovascular disease. The percentage of patients with malnutrition according to the SGA decreased significantly over the course of the treatment (Table 1). Patients with severe malnutrition (SGA C) decreased from 30.4% at baseline (34 patients) to only 3% (2 patients) at 24 weeks.

Blood glucose and HbA1c levels were significantly reduced at 12 and 24 weeks, while no statistically significant changes were found in cholesterol, triglycerides, creatinine or glomerular filtration rate. There was a significant increase in the variables related to nutritional status: weight, BMI, albumin, prealbumin and transferrin. During follow-up, CRP levels reduced significantly and the CRP/albumin ratio decreased (Table 1). There were no significant differences in relation to the patient's place of residence (home or institution). In terms of gastrointestinal tolerance, a small number of patients had moderate/severe symptoms and there was no change during follow-up. The percentage of patients with no gastrointestinal symptoms increased from 73% at baseline to 88.6% at 12 weeks and 97.1% at 24 weeks ($p < 0.001$). The most common gastrointestinal complication was constipation, with no significant changes over the follow-up period (Table 2).

Discussion

Diabetes is an increasingly prevalent disease in the Western world. In Spain, it has been estimated from the Di@bet.es study data that 13.8% of the Spanish population has diabetes and 30% may have some carbohydrate metabolism disorder.[4] Malnutrition is frequently associated with diabetes.[5] In a recent study, the prevalence of DM in patients receiving EN was 31.8% and more than 85% of the patients received a specific formula for diabetes.[6] Several studies have shown the effectiveness of these formulations in controlling basal blood glucose in short and intermediate-length periods (<12 weeks) in patients with diabetes.[2,3,7,8] Their use has also been associated with a significant reduction in healthcare costs.[9] However, the available meta-analyses[10–12] have

Table 2 Baseline gastrointestinal symptoms and changes at 12 and 24 weeks.

Visits	Baseline	12 weeks	24 weeks
No moderate/severe gastrointestinal symptoms (%)	73.0	88.6	97.1
Mild nausea (%)	0	9.8	2.7
Moderate/severe nausea (%)	0.9	0.9	0
Mild vomiting (%)	0	3.6	0.9
Moderate/severe vomiting (%)	0	0	0
Mild regurgitation (%)	0	14.3	11.6
Moderate/severe regurgitation (%)	0	1.8	0
Mild constipation (%)	0	6.3	12.5
Moderate/severe constipation (%)	14.3	12.5	5.4
Mild diarrhoea (%)	0	8.0	6.3
Moderate/severe diarrhoea (%)	0	1.8	3.6
Mild flatulence (%)	0	14.3	13.4
Moderate/severe flatulence (%)	10.7	0.9	1.8
Mild abdominal distension (%)	0	14.3	13.4
Moderate/severe abdominal distension (%)	0	0	1.8
Mild abdominal pain (%)	0	3.6	6.3
Moderate/severe abdominal pain (%)	0	0	0

only been able to assess a small number of studies, with few patients and always in the short term (less than 3 months), concluding that more studies are needed on this subject.

In the most recent meta-analysis by Sanz-París et al.,[12] only 18 studies were included that used formulas rich in monounsaturated fats (MUFA), defined as those that provide >20% of their total calorific value as MUFA, as in the formula used in our study. Only three studies evaluated patients after more than one month, but even then the follow-up time was short, at 70[3] and 84 days,[7,8] respectively. Our study has the limitation of not being an interventional clinical trial comparing a specific formula, but observational in real life without a control group. However, that is also precisely our strength; the fact that the study was conducted in real clinical practice, and that it was multicentre and included a significant number of people with long-standing diabetes over an extended period of 24 weeks. Moreover, all the patients completed the follow-up period. To our knowledge, no study of specific formulations in diabetes has had such long-term follow-up.

The meta-analysis by Sanz-París et al[12] showed that formulas rich in MUFA lead to a reduction in HbA1c of −0.63% (95% CI −1.21 to −0.05) compared to standard formulas. However, there was considerable heterogeneity between the studies evaluated; among other things, they refer to patients receiving EN both by tube and by oral supplementation. Our data, only from patients fed by tube, also showed good blood glucose control when assessed by HbA1c, which was 7.1% at the end of follow-up, and also showed a significant reduction over the follow-up period of −0.6%, similar to that reported in the Sanz-París et al. meta-analysis.[12] Taking into account the mean age of 75, the long time since onset of DM and the frequency of chronic complications in our series, we can consider the degree of control achieved as very good. We therefore conclude that, in a real-life context, our data confirm the favourable effect of specific formulas in achieving good blood glucose control.

The lipid profile did not change in our study over 24 weeks, with levels that can be considered adequate from the initial visit. Although the use of specific formulas has been associated with lower levels of triglycerides compared to the standard formula,[12,13] we were not expecting any change in lipid parameters in our case. There were also no significant changes in renal function. The formula being high in both calories and protein could give rise to reservations about its effects on hydration, due to the potential for worsening kidney function, but our group has already demonstrated the safety of concentrated formulas.[14]

The percentage of patients with malnutrition according to the SGA decreased significantly over the course of the treatment, as was to be expected with the medical nutrition therapy. Patients with severe malnutrition decreased from 30.4% at baseline to only 3% at 24 weeks, and any degree of malnutrition from 78.6% to 29.9%, confirming the effectiveness of the formula, as we expected. The improvement in nutritional status is parallel to a weight gain of more than 2 kg and an improvement in both plasma protein levels and the CRP/albumin ratio, which has been advocated as a marker of morbidity and mortality.[15] Last of all, we would like to highlight the good tolerance to the formula, with a progressive increase in the percentage of patients without any gastrointestinal symptoms. Moreover, the fact that there was no loss of patients due to discontinuation of the formula suggests that the overall tolerance during the six-month follow-up must have been good.

In conclusion, our real-life study confirms that the use of a high-protein, high-calorie formula specific for diabetes for six months of nutrition therapy enables adequate blood glucose control and improvement in nutritional status, with good gastrointestinal tolerance.

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Conflicts of interest

María D. Ballesteros Pomar has received honoraria for lecturing, consulting or research studies from Fresenius Kabi, Nestlé Health Science, Abbott Nutrition, Nutricia, Vegenat and Novo Nordisk.

Beatriz Lardiés Sánchez has received honoraria for lecturing, consulting or research studies from Fresenius Kabi, Nestlé Health Science, Abbott Nutrition, Nutricia, Persan, Novo Nordisk, Lilly, Boehringer, Sanofi, AstraZeneca, Gebro Pharma and Mylan.

María Argente Pla has received honoraria for lecturing or research studies from Fresenius Kabi, Nestlé Health Science and Abbott Nutrition.

Araceli Ramos Carrasco has received honoraria for research studies from Fresenius Kabi, Nestlé Health Science, Abbott Nutrition, Nutricia and Vegenat.

Lorena Suárez Gutiérrez has received honoraria for lecturing, consulting or research studies from Fresenius Kabi, Nestlé Health Science, Abbott Nutrition, Vegenat, Novo Nordisk, Amgen, Sanofi, Jamsen, AstraZeneca, Takeda, MSD and Novartis.

Alfredo Yoldi Arrieta has received honoraria for lecturing from Astra and Novo Nordisk.

Patricia Sorribes Carreras has received honoraria for presentations in the area of dysphagia from Fresenius Kabi.

Sonsoles Gutiérrez Medina has received honoraria from Fresenius Kabi, Nutricia, Novo Nordisk, Lilly, Sanofi and AstraZeneca.

Juan Bautista Molina Soria has received honoraria for lecturing, consulting or research studies from Fresenius Kabi, Nestlé Health Science, Abbott Nutrition, Nutricia, Vegenat and Persan.

María Berrio Miranda has received honoraria for lecturing or research studies from Fresenius Kabi, Abbott Nutrition, Nutricia and Lilly.

M. Socorro Leyva Martínez has received honoraria for lecturing or research studies from Fresenius Kabi, Abbott Nutrition, Nutricia and Lilly.

Oscar Torregrosa Suau has no conflicts of interest.

M. Teresa Oliván Usieto has no conflicts of interest.

Francisco Villazón González has received honoraria for lecturing from Amgen, Fresenius Kabi, Nutricia and Abbott Nutrition.

Jimena Abilés Osinaga has no conflicts of interest.

Esteban Martín Echevarría has received honoraria for lecturing or research studies from Fresenius Kabi, Nestlé Health Science, Novo Nordisk, Nutricia and Persan Farma.

Katherine García-Malpartida has received honoraria for lecturing or consulting from Fresenius-Kabi, Nestlé Health Science, Abbott Nutrition, Nutricia and Persan Farma.

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